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Letter to the Editor

# Proton pump inhibitor treatment decreased duodenal and esophageal eosinophilia in a case of eosinophilic gastroenteritis

*Dear Editor*

Primary eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE), exclusively affect the gastrointestinal tract with eosinophil-predominant inflammation, where gastrointestinal eosinophilia secondary to other diseases, such as drug-induced and parasitic disorders, have been excluded.[1] In addition, EoE occasionally occurs secondary to EGE.

As recently suggested in U.S. guidelines for EoE,[2,3] when EoE suspected by clinical and pathological findings responds well to proton-pump inhibitors (PPIs), it is distinguished from typical EoE as a newly recognized entity known as PPI-responsive esophageal eosinophilia (EE) (PPI-REE). Therefore, PPI trials using high-dose PPIs are recommended as a first-line therapy or diagnostic tool to distinguish PPI-REE from EoE. The effect of PPIs for gastrointestinal eosinophilia, except for PPI-REE, remain unknown. Here, we report a case of EGE associated with duodenal and esophageal eosinophilia successfully treated with a PPI.

## Case report

A 2-year and 7-month-old girl underwent upper gastrointestinal endoscopic examination at our hospital for a follow-up. She had been diagnosed with EGID associated with duodenal eosinophil infiltration at 11 months of age.[4] Elemental diet (ED) caused rapid weight gain and improved tracheal aspiration and esophageal clearance, but duodenal eosinophil infiltration persisted. The exacerbation of symptoms was not observed, and the ED was replaced with enteral formula, although she required the tubing of enteral formula because of difficulty in or reluctance to oral intake.

On upper gastrointestinal endoscopic examination, biopsies showed EE that had not been previously detected and persistent duodenal eosinophil infiltration with 106 eosinophils/high power field (HPF) and 72 eosinophils/HPF, respectively (Fig. 1A, B, respectively). According to the U.S. guideline for EoE,[2,3] a PPI trial using oral lansoprazole (up to 30 mg/day) was begun in a subsequent clinic visit to determine her response. After PPI-treatment initiation, the patient's appetite improved, and subsequently, her amount of oral food intake increased gradually. Five months after starting PPI treatment, tube feeding was discontinued, and reevaluation of upper endoscopy was concurrently performed for pathological evaluation after PPI treatment. Duodenal eosinophilia and EE detected in the prior examination had drastically improved (Fig. 1C, D, respectively). Afterwards, she consumed sufficient amounts of a variety of foods. Eight months after terminating tube feeding, PPI was tapered and discontinued. At the time of reporting this case, she remains symptom-free with a regular diet and no PPI treatment.

## Discussion

Although a recent report showed that PPI-REE possesses significant molecular overlap with EoE,[5] it remains to be determined if PPI-REE represents a subtype of EoE, a gastroesophageal reflux disease-associated condition, or a unique entity. In addition, the possible mechanisms of PPI action in EE[5] may be a direct anti-inflammatory effect via blockade of IL-4– and IL-13–stimulated secretion of eotaxin-3[6] and healing of disrupted epithelium as well as acid suppression, which may shorten eosinophil viability by increasing pH. Indeed, this patient's pH monitoring at first admission was negative. Taken together, although EE secondary to EGE may be much different from the conditions described above, PPI appears to be a promising treatment for this condition. In the present case, during the initial treatment, ED did not lead to complete remission, whereas PPI completely improved both clinical and histological findings. More surprisingly, the duodenal as well as esophageal eosinophil infiltrations nearly disappeared. Duodenal eosinophilia in this patient had never been improved well before. This may suggest that PPI also blocks the activation of STAT6 directly by IL-4 and IL-13 in the duodenal epithelium, since this inhibitory effect is not specific for esophageal epithelium and may be observed in many other cell lines.[7] Measurements of gastrointestinal cytokine levels (such as with the string test) and pH in peri-PPI trials may be also important in revealing mechanisms.

A PPI trial may be the only way to distinguish PPI-REE from EoE because of their clinical and histological similarity. Therefore, the long-term prognosis of PPI-REE could vary. PPI alone may not be sufficient to induce complete remission; combining PPI with prior ED treatment might be required. Additionally, there is a possibility that ED did not induce complete remission due to other inflammatory conditions, such as *Helicobacter pylori* infection, as well as allergy, although the patient's allergy status was unclear. In order to dissect these mechanisms, allergy tests, such as the allergen-specific lymphocyte stimulation test and pylorus infection test, should be performed if the patient's EGIDs recur.

Two major treatments for EGE are considered in most cases.[1] One is the use of corticosteroids such as prednisolone. Additionally, especially in children, dietary eliminations have often been chosen

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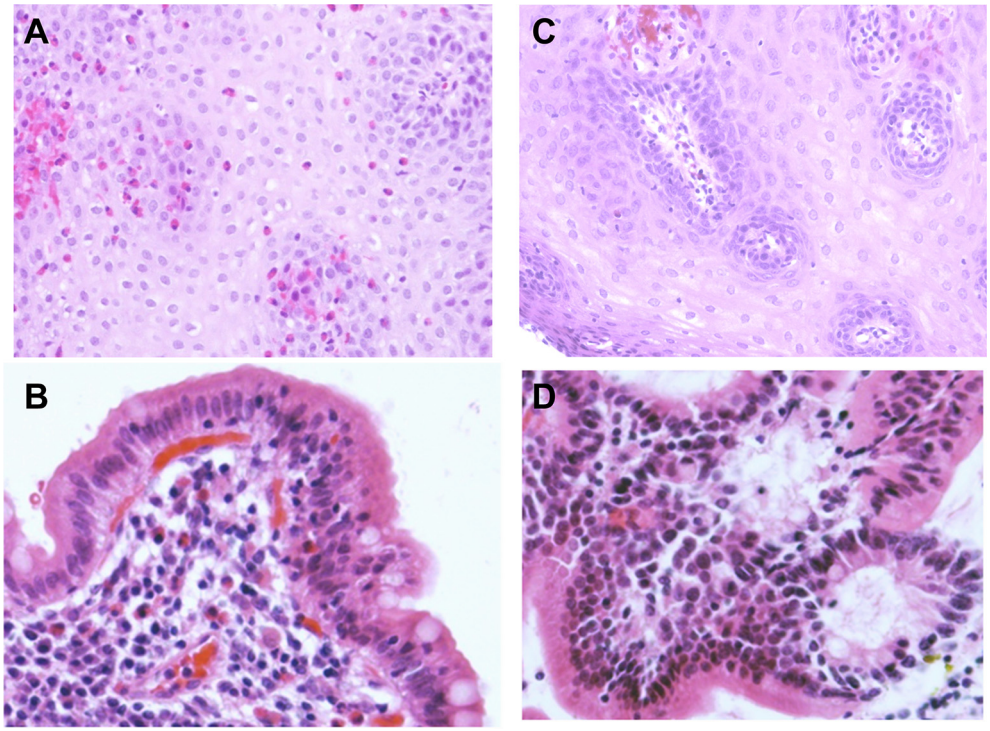


**Fig. 1.** Histological findings of esophagus and duodenum stained with H.E. before and after PPI-treatment. (A) Esophageal and (B) duodenal eosinophil infiltrations with 106 eosinophils/high power field (HPF) and 72 eosinophils/HPF respectively, are shown in pretreatment biopsies. (C) and (D) indicate esophagus with 1 eosinophil/HPF and duodenum with 3 eosinophils/HPF after PPI-treatment, respectively (Original optical magnifications: ×200 in all figures).

for the treatment of EGE.[8] When the possible causative foods are unknown or the effects of their elimination are restricted, amino acid-based EDs are used, often resulting in complete remission.[1] Therefore, ED was initially used, and the response was favorable in this case. However, difficulty in or reluctance to oral intake that may be associated with EGID[4] and tissue eosinophilia remained, and our patient showed the first signs of improvement of them with PPI treatment, suggesting that PPI could promise a certain level of additive or synergistic effect with ED or dietary modifications.

Only nonspecific inflammation had been observed in her esophagus before. Usually, more than three esophageal biopsies are taken evenly from the proximal to distal esophagus in our hospital. Consequently, it is unlikely that we missed EE. EE can be a part of the findings of EGE and discovered during the course of EGE. Interestingly, there are previous reports of unusual cases of EGE in patients who had eosinophil infiltration, preferentially not in the epithelium but in the deep mucosal and submucosal layers of the esophagus[9] or gastric muscularis,[10] meaning that esophageal eosinophil infiltration can sometimes be primarily observed in places other than the superficial mucosa.

In conclusion, we describe a patient with an initial diagnosis of EGID with duodenal eosinophilic infiltration who developed EE during follow-up. PPI treatment used for the concurrent EE unexpectedly resulted in eradicating the duodenal eosinophilia as well as the EE, and overall symptomatic improvement was also observed. PPI treatment can be a promising additive approach even for EGE.

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*Conflict of interest*

The authors have no conflict of interest to declare.

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